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EXAMINER
TURNER, SHARON L

ART UNIT	PAPER NUMBER
1647	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/723,544	SCHENK ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-95* is/are pending in the application.

4a) Of the above claim(s) *71,73,76 and 79-95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69,70,72,74,75,77 and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *69-95* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 November 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. If applicant desires priority under 35 U.S.C. 119(e) and 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicant's transmittal papers indicate priority as a CIP of 09/201,430 and of provisional 60/080,970. However, the first paragraph of the specification only reference the case as a continuation of 09/580,018 and as a CIP of 09/322,289.

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Instant specification is a continuation of 09/580,018 and shares the same disclosure. However, priority is claimed based upon 09/322,289 which disclosure apparently differs in that the '289 application fails to support instantly claimed chimeric peptides. Thus, the priority date awarded instant claims (effective filing date) is the filing date of the '018 case, 5-26-00. Traversal should include reference to the '289 application where support may be found for the instantly claimed chimeric peptides and immunogenic compositions.

Drawings

3. Figure 11 is objected to because the figure fails to specify the treatment groups via an appropriate key referencing those groups denoted by the symbols, i.e., open square, diamond, circle etc. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Election/Restriction

4. Applicant's election with traverse of Group I, to the extent of internal cleavage product Aβ1-3, T helper cell epitope derived from diphtheria toxoid, and N terminal of the first 3 amino acids of Aβ in Paper No. 11 is acknowledged. The traversal is on the ground(s) that particular claims are written in generic format and not Markush style format, that the subject matter is shared to the extent that portions of the beta amyloid sequence or T helper cell epitopes are similar in structure and that the multiple sequences should more properly be treated as species. This is not found persuasive because the claims are directed to mutiple patentably distinct inventions. The peptides

share uncommon structure in that the genus is variable. A search for any one particular chimeric molecule would not reveal all pertinent prior art to any other of the other chimeric molecules. The genus is not of a single shared structure but to multiple sub-generic elements. As the inventions so differ they can not be considered species that may be encompassed by a single search. Thus the inventions lack unity. Rejoinder would only be considered as to elements where the core structure is shared in common. The requirement is still deemed proper and is therefore made FINAL.

5. Claims 71, 73, 76 and 79-95 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Double Patenting

6. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and In re Goodman, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 69-70, 72, 74-75 and 77-78 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 09/724,570, claims 89-98 of copending Application No. 09/723,927, claims 1-7, 44-45, 48 and 65 of copending Application No. 09/497,553, claim 65 of copending Application No. 09/724,477, claims 102-109 of copending Application No. 09/724,489, claims 33-37 of copending Application No. 09/580019, claims 1-10 of copending Application No. 09/585,817, 09/724,567, 09/724,575, 09/724,953, 09/724,570 and 09/979,952. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious over the copending claims in each of the aforementioned applications.

In particular all claims are drawn to peptides, pharmaceutical or immunogenic compositions comprising peptides. Instant claims are viewed as being the broadest claims amongst the co-pending applications as the peptides comprise the broadest variability with respect to sequence structure and the immunogenic compositions merely comprise the peptide with either an acceptable carrier, excipient, diluent or adjuvant. The peptides of instant claims diverge from beta-amyloid or various plaque forming peptides as claimed in the copending cases. Thus, the copending peptides and/or peptide compositions are species or sub-genera of the instant peptides that are completely encompassed within the larger genus of instant claims.

Further, as all peptides are immunogenic to some extent and as all peptides for laboratory manipulation are provided to the artisan in some form of suitable carrier, excipient, diluent or adjuvant, the copending compositions and functional language as to providing an immune response would either anticipate or render obvious instant claims directed to peptides with T helper cell epitopes that effect immune responses and to

immunogenic compositions comprising the peptides. The particular compositions of the copending claims as to adjuvants are species that anticipate the compositions of instant claim 77. To the extent that the copending claims do not specifically recite alum as in claim 78, the artisan nevertheless recognizes that such is a suitable adjuvant choice for effecting an enhanced immune response with coadministration of a peptide. Thus, the copending claims are all directed to particular species or sub-genera of the instantly claimed larger genus claims. The copending claims if issued first would be completely encompassed within instant claims and the copending claims if issued first would serve as a species or subgenus capable of anticipating the broader claims of instant genus. Thus, the copending claims are subject to obviousness-type double patenting rejections.

This is a provisional obviousness type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 69-70, 72, 74-75 and 77-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Instantly pending claims are as amended 6-14-02. In particular, the claims are newly drawn to chimeric peptides and immunogenic compositions. This amendment points to support for the recitations of new claim 69 at pp. 10, 13-14 and 28-32. However, review of the specification at such pages fails to provide support for the recitations as follows. Claim 69 as amended recites: A chimeric peptide having a first portion and a second portion, wherein the carboxyl terminus of the first portion is linked to the amino terminus of the second portion; and, wherein the first portion is from the free N-terminus of a naturally-occurring internal peptide cleavage product which, when naturally occurring in a mammal, is derived from a precursor protein or a mature protein and the second portion comprises a T helper cell epitope; or, wherein the first portion comprises a T helper cell epitope and the second portion is from the free C-terminus of said naturally occurring internal peptide cleavage product. The specification does not apparently support the breadth of peptides now contemplated.

In particular, no support is found for the breadth of peptides within "the first portion" as "from the free N-terminus of a naturally-occurring internal peptide cleavage product which, when naturally occurring in a mammal, is derived from a precursor protein or a mature protein", the particular linkage of the first portion and the second portion, and the breadth of peptides contemplated in the second portion as drawn to "T helper cell epitipes". Further with respect to the second portion of the claim, the specification does not apparently support the breadth of peptides wherein the second portion is from the "free C-terminus of said naturally occurring internal peptide cleavage product", the particular linkage and to the first portion and wherein the first portion has

"T helper cell epitopes". Further, the specification does not apparently support the recitation of "an immunologically effective amount" as recited in claims 77-78 or for the recitation of "alum" in claim 78. Thus, the recitations constitute new matter absent particular evidence for their support.

9. Claims 69-70, 72, 74-75 and 77-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification describes a polypeptide sequence consisting of beta-amyloid 1-42 and beta amyloid 1-5 conjugated to sheep anti-mouse IgG which are disclosed as exhibiting beta amyloid plaque clearing activity in PDAPP mice, see in particular pp. 60-64 of the specification. It is also apparent from the specification that the artisan was in possession of other particular beta amyloid peptides and peptide conjugates capable of stimulating antibody reactive to beta-amyloid, see in particular specification p. 60-61. While not capable of clearing amyloid plaques, these peptides and/or immunogenic compositions were useful for the purpose of stimulating beta-amyloid specific antibodies for detection of Abeta peptides and/or Alzheimer's plaques.

The claims are also directed to peptides comprising a second portion that is a suitable "T helper cell epitope". T helper cell epitopes are generally known to be peptides capable of stimulating the release of lymphokines that activate B cells thus stimulating an enhanced B cell (antibody) response. While the artisan is apprised of

particular T helper cell epitopes as disclosed in the prior art, the artisan recognizes that a substantial number of such peptides capable of eliciting Th function remain to be determined or discovered. Moreover, the specification and art fails to disclose any definitive structure or definitive assay whereby Th cell activity is determined. Instead the structures amongst different peptides, with different MHC molecules and different art recognized assays (cytokine stimulation, T cell proliferation etc.) for determining function vary substantially. In addition, the specification does not apparently provide for any particular diphtheria T helper cell epitopes, describe their particular characteristics either structurally or functionally. While the artisan is provided with particularly known T helper cell epitopes of the prior art including as disclosed at p. 28, the claims do not adequately describe by structure all known T-helper cell epitopes amongst all possibly known sequences. The specification and claims fail to delineate those structural and/or functional requirements of peptides described as T helper cell epitopes. While the artisan has multiple assays to measure T cell reactivity or antibody production (suitable measurements of T helper cell eptiope activity), see for example specification p. 10, lines 12-29, no particular structural and or functional features or assays are denoted as being definitive of the recitation as claimed.

The claims encompass peptides comprising a "first portion from the free N-terminus of a naturally-occurring internal peptide cleavage product which, when naturally occurring in a mammal, is derived from a precursor protein or a mature protein" and a second portion comprising "a T helper cell epitope ". Yet, the specification fails to adequately describe that which is "the free N-terminus of a naturally

–occurring internal peptide cleavage product which, when naturally occurring in a mammal is derived from a precursor protein or a mature proteins," because the specification and claims fail to distinguish the required structural features or any method of determining the suitable peptides or peptide sequences. The artisan must be able to determine if any particular sequence meets this limitation of the claims, including whether a peptide is suitably derived from a naturally-occurring molecule, encompassing allelic forms. Yet to the extent that the sequence is merely derived from a multitude of mammalian peptides, naturally occurring variants and to sequences that are unlimited in length, the artisan is left with little understanding of either the structural and/or functional features required. With respect to the free N-terminus, the specification is only exemplary to a few beta-amyloid sequences.

Thus the specification provides inadequate written description with respect to these recitations. The instant disclosure of a few single polypeptides with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. It is further noted that no function is required of the chimeric peptides. As to the immunogenic compositions, no particular immune function is denoted as being required. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc.,

107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus may be achieved by means of a recitation of a representative number of members falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. In the instant case the claims appear to encompass peptides in which the first portion is of nearly unlimited structure without function while the second portion is loosely limited to several (as generically claimed) functional recitations without any particular structural guidance. Thus, neither the specification, prior art nor claims provides sufficient structural and/or functional correlative teachings to enable one of skill to identify the polypeptides encompassed by either the first portion

or the second portion. Without suitable description of the first and second portion members, the chimeric peptides and immunogenic compositions lack adequate written description support such that the artisan is apprised that applicant was in possession of the invention claimed with peptides comprising such first and second portions. There is no fulfilling structural and/or functional requirements for the chimeric peptides and their immunogenic compositions.

10. Claims 69-70, 72, 74-75 and 77-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing beta-amyloid plaque burden in PDAPP transgenic mice which over-express amyloid by administration of beta amyloid 1-42 peptide (AN1792) and beta amyloid 1-5 peptide conjugated to sheep anti-mouse IgG, see in particular pp. 60-64, or for providing particular peptides capable of stimulating beta-amyloid specific antibodies, does not reasonably provide enablement for the chimeric peptides or immunogenic compositions as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The claims are drawn to various chimeric peptides and immunogenic compositions. The peptides and compositions are disclosed as useful in the prevention

or treatment of diseases, particularly of the nervous system including diseases associated with amyloid deposits of Aβ or for stimulating amyloid specific antibodies. The utility of the peptides and compositions is based upon findings which show particular strategies of targeting plaque removal via antigen or antibody administration and for labeling amyloid plaques. Evidence that such therapy can be effective in the removal of amyloid plaque burden or in detection of amyloid plaques is exhibited in applicant's specification.

However, what the specification does not teach is the scope of antigen/antibody variability effective to promote plaque removal or clearance or that enables amyloid specific antibody production. In particular neither instant specification nor the art recognizes treatment or detection with the broad scope of chimeric peptides and immunogenic compositions now claimed wherein the multitude of the compositions differ substantially in sequence structure, length and the ability to mediate particular immune responses.

The specification teaches at pp. 60-64 that administration of aggregated beta amyloid 1-42 peptide (AN1792) and beta amyloid 1-5 peptide conjugated to sheep anti-mouse IgG is effective at reducing beta-amyloid levels within the brains of mice which are transgenic for PDAPP. In particular these results are noted at p. 63, line 30-p 64, line 20. However, the specification further reveals that conjugates of other beta-amyloid peptides were insufficient to produce any reduction in beta-amyloid plaque accumulation. Such results evidence the unpredictability in the art with respect to effecting an adequate immune response with members of the chimeric peptides and

immunogenic compositions claimed. The specification fails to evidence any means for determining a priori which of the encompassed sequences reliably and predictably provide for such beneficial use.

Moreover, the claims are directed to peptides comprising a "first portion from the free N-terminus of a naturally-occurring internal peptide cleavage product which, when naturally occurring in a mammal, is derived from a precursor protein or a mature protein" and a second portion comprising "a T helper cell epitope ". Yet, the specification fails to adequately describe that which is "the free N-terminus of a naturally –occurring internal peptide cleavage product which, when naturally occurring in a mammal is derived from a precursor protein or a mature proteins," because the specification and claims fail to distinguish the required structural features. The artisan must be able to determine if any particular sequence meets this limitation of the claims. Yet to the extent that the sequence is merely derived from a multitude of mammalian peptides and is unlimited in length, the artisan is left with little understanding of either the structural or functional features required. With respect to the first portion, the specification is only exemplary to a few beta-amyloid sequences.

Moreover, while the artisan is provided with particularly known T helper cell epitopes of the prior art, the claims do not adequately describe by structure all known T-helper cell epitopes amongst all possibly known sequences. The specification and claims fail to delineate those structural and/or functional requirements of the peptides described as T helper cell epitopes. While the artisan has multiple assays to measure T cell reactivity, see for example specification p. 10, lines 12-29, no particular structural

and or functional features or assays are denoted or recognized in the art as being definitive of the recitation. Such is akin to a single means claim i.e., where a means recitation does not appear in combination with another recited element of means and is subject to an undue breadth rejection under 35 USC 112, first paragraph because the specification at most would only disclose those means known to the inventor at the time of the invention, see in particular MPEP 2164.08(a).

The skilled artisan further recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech.,18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that immunological responses depend upon the particular antibody molecule. In particular, antibody recognition occurs via antibody variable and constant regions, see in particular Benjamini, Wiley Liss, 1991, pp. 49-65 and Table 5.1. Each antibody molecule is unique with respect to it antigen and the biological function which it is capable of eliciting within a host, see in particular Benjamini, pp. 49-50 and Table 5.1. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined.

Thus, the specification does not enable the broad scope of the claims that encompasses various chimeric peptides and immunogenic compositions because the specification does not teach the specificity required. Moreover, while the artisan recognizes that particular peptide peptide immunogens may be "universally" useful for stimulating an immune response i.e., as adjuvant or Th eptiopes may be, these peptides are not immediately provided but instead are generically claimed by the recitation of a T helper cell epitope.

Instead the artisan must make and then determine the utility of any particular chimeric peptide or immunogenic composition. While it would not be undue to make any particular peptide sequence possible, such does not fulfill the ability to use any peptide sequence possible. The specification does not correlate the breadth of the peptides encompassed to their respective uses. For example, given the breadth of the sequences it would not be surprising that particular peptides encompassed by the claims would be incapable of stimulating any reactivity to beta-amyloid. As the specification is written in context of this utility for diagnosis, detection and development of pharmaceuticals for the treatment of Alzheimer's, the artisan would be left unapprised of such divergent molecules' respective use.

Thus, for the aforementioned reasons, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed chimeric peptides and immunogenic compositions in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the

changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue experimentation to make and use the claimed invention.

Claim Rejections - 35 USC § 102 and 103

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claim 69, 75 and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Sad et al., Vaccine, 11(11):1145-1149, 1993.

Sad et al., teach chimeric peptide conjugates of syntheic gonadotrophin-releasing hormone and diphtheria T helper cell epitopes. In particular the Sad peptide meets instant limitations in that the peptide is chimeric, possesses a first portion GnRH comprising a free N-terminus of the naturally occurring internal peptide cleavage product derived form the mature GnRH protein (after signal sequence cleavage) and a

second portion comprising diphtheria toxin T helper cell epitopes, see in particular p. 1146, columns 1-2. The reference also notes GnRH conjugates to diphtheria toxin, see in particular p. 1145, column 2, first paragraph. The peptide conjugates were administered as saline emulsified freund's adjuvant compositions or as adsorbed peptides on calcium phosphate, see in particular p. 1146-1147. Thus, the reference teachings anticipate the claimed invention.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 69-70, 72, 74, 75 and 77-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al., US 5,750,349 (May 12, 1998), Stevens et al., US 4,713,366(Dec. 15, 1997) and Lehrer et al., US 5,464,823 (Nov. 7, 1995) as evidenced by Thomas et al., US 6,284,533 (Sept. 4, 2001).

Suzuki et al., teach antibodies to beta-amyloid generated via the use of peptide immunogens comprising various portions or derivatives of beta-amyloid, see in particular Disclosure of Invention, columns 3-13. In particular the portions include the N- or C-terminus of beta-amyloid (a naturally occurring internal peptide cleavage product which when naturally occurring in a mammal is derived from a precursor protein or a mature protein) derived from the mammalian protein amyloid precursor protein, see in particular Abstract and Background Art, columns 1-3 in the context of claims. Such immunogen peptides are noted in SEQ ID NO's:1-7 and 10 as having a portion of beta amyloid residues 1-3, Asp-Ala-Glu as recited in claim 72. The peptides antigens are produced bound to or adsorbed to appropriate carriers for immunization including with adjuvants and are immunogenically effective to produce antibodies, see in particular column 15, lines 1-53 (claim 77). Suzuki teaches that the antibodies derived from the disclosed immunogens are useful in the detection and diagnosis of diseases related to beta-amyloids including Alzheimer's and for the development of preventive-therapeutic compositions.

However, Suzuki et al., do not teach the chimeric peptide claimed wherein the carboxyl terminus of the first portion is linked to a T helper cell epitope (claim 69), binds multiple MHC molecules (claim 74), is derived from diphtheria toxoid (claim 75) and wherein the adjuvant is alum (claim 78)

Stevens et al., 4,713,366 teach antigenic modification of polypeptides wherein the sequence is coupled or linked to diphtheria toxoid and immunogenic compositions wherein the adjuvant is alum, see in particular column 23, lines 12-53, column 37, lines 3-50, column 38, line 51-column 39, line 7, column 44, line 42-column 45, line 4, column 46, lines 35-57, column 79-80, Table 13, column 81, lines 39-57, column 82, lines 66-column 83, line 3 and column 87, lines 36-55.

Lehrer et al., US 5,464,823 similarly teach methods for producing antibodies including via linkage with suitable carriers including diphtheria toxoid. In particular, at column 9, lines 39-58 states, "Antibodies to the protegrins of the invention may also be produced using standard immunological techniques for production of polyclonal antisera and, if desired, immortalizing the antibody-producing cells of the immunized host for sources of monoclonal antibody production. Techniques for producing antibodies to any substance of interest are well known. It may be necessary to enhance the immunogenicity of the substance, particularly as here, where the material is only a short peptide, by coupling the hapten to a carrier. Suitable carriers for this purpose include substances which do not themselves produce an immune response in the animal to be administered the hapten-carrier conjugate. Common carriers used include keyhole limpet hemocyanin (KLH), diphtheria toxoid, serum albumin, and the viral coat protein of rotavirus, VP6. Coupling of the hapten to the carrier is effected by standard techniques such as contacting the carrier with the peptide in the presence of a dehydrating agent such as dicyclohexylcarbodiimide or through the use of linkers such as those available through Pierce Chemical Company, Chicago, Ill."

While Stevens et al., and Lehrer et al., are silent as to diphtheria toxin's

properties as T helper cell epitiopes and the ability to bind multiple MHC molecules, such is evidenced by Thomas et al., US 6284533.

In particular, Thomas teaches particular peptides such as diphtheria toxoid that provide universal T helper cell epitopes capable of binding multiple MHC molecules as follows:

at column 5, lines 21-58;

"The immunogenic fusion polypeptide encoded on a plasmid as described herein comprises a T cell epitope portion and a B cell epitope portion. A T cell epitope portion encoded on the plasmid of this invention comprises a non-endogenous CETP protein, or fragment thereof, that contains a broad range or "universal" helper T cell epitope which binds the antigen presenting site of multiple (i.e., 2, 3, 4, 5, 6 or more) class II major histocompatibility (MHC) molecules and can form a tertiary complex with a T cell antigen receptor, i.e., MHC:antigen:T cell antigen receptor. By "non-endogenous CETP protein" is meant a protein which is not the endogenous CETP of the individual who is to be administered a plasmid of this invention. Such non-endogenous CETP proteins, or fragments thereof, useful as T cell epitope portions of the immunogenic fusion polypeptide encoded by plasmids of this invention include tetanus toxoid (particularly peptides of tetanus toxoid having amino acid sequences of amino acids 2-15 of SEQ ID NO:7 and amino acid sequence of SEQ ID NO:10); diphtheria toxin (particularly peptides having amino acid sequences of amino acids 271-290, 321-340, 331-350, 351-370, 411-430, and 431-450 of SEQ ID NO:9); class II MHC-associated invariant chain; influenza hemagglutinin T cell epitope; keyhole limpet hemocyanin (KLH); a protein from known vaccines including pertussis vaccine, the Bacile Calmette-Guerin (BCG) tuberculosis vaccine, polio vaccine, measles vaccine, mumps vaccine, rubella vaccine, and purified protein derivative (PPD) of tuberculin; and also synthetic peptides which bind the antigen presenting site of multiple class II histocompatibility molecules, such as those containing natural amino acids described by Alexander et al. (Immunity, 1: 751-761 (1994)). When attached to a CETP B cell epitope portion, the T cell epitope portion enables the immunogenic fusion polypeptide to break tolerance in order for antibodies to be made that react with endogenous CETP. By "breaking tolerance" is meant forcing an organism to mount an immune response to a protein, such as endogenous CETP, that the organism does not normally find immunogenic.

at column 10, lines 26-40;

Broad range antigenic helper T cell epitopes are known in the art. These include, for example, epitopes of tetanus toxoid (TT) and diphtheria toxoid (DT) (see, for example, Panina-Bordignon, P., et al., Eur. J. Immunol., 19: 2237-2242 (1989) (characterization of universal tetanus toxoid helper T cell epitope peptides); Etlinger, H.,

Immunol. Today, 13: 52-55 (1992); Valmori, D., et al., J. Immunol., 149: 717-721 (1992) (use of universal TT epitopes in candidate anti-malarial vaccine); Raju et al., Eur. J Immunol., 25: 3207-3214 (1995) (broad range T cell epitopes of DT); Talwar, G. P., et al., Proc. Natl. Acad. Sci. USA, 91: 8532-8536 (1994) (use of TT and DT as universal epitopes in anti-human chorionic gonadotropin vaccine); Talwar, G. P., et al., Proc. Natl. Acad Sci. USA, 91: 8532-8536 (1994)).

at column 10, line 57-column 11, line 14;

Plasmids of this invention may encode a variety of non-endogenous CETP proteins, or fragments thereof, such as tetanus toxoid, particularly peptides of tetanus toxoid having amino acid sequences of amino acids 2-15 of SEQ ID NO:7 (a corresponding nucleotide coding sequence is nucleotides 13-54 of SEQ ID NO:5) and amino acid sequence of SEQ ID NO:10. Another source of universal or broad range T cell epitopes useful in the plasmids of this invention is diphtheria toxin, particularly peptides having amino acid sequences of amino acids 271-290, 321-340, 331-350, 351-370, 411-430, and 431-450 of SEQ ID NO:9. An example of corresponding nucleotide sequences encoding these broad range T cell epitopes from diphtheria toxin are nucleotides 811-870, 961-1020, 991-1050, 1051-1110, 1231-1290, and 1291-1350 of SEQ ID NO:8, respectively. Other sources of universal or broad range T cell epitopes that may be encoded on plasmids of this invention include, but are not limited to, class II MHC-associated invariant chain; hemagglutinin; keyhole limpet hemocyanin (KLH); a protein from known vaccines including pertussis vaccine, the Bacile Calmette-Guerin (BCG) tuberculosis vaccine, polio vaccine, measles vaccine, mumps vaccine, rubella vaccine, and purified protein derivative (PPD) of tuberculin; and also synthetic peptides as described by Alexander et al. (1994).

at column 20-21, Example IV;

The results of the above experiment using a rabbit model for atherosclerosis indicate that the plasmid-based vaccines of this invention may be used to prevent or treat atherosclerosis in other vertebrates. By analogy to the treatment for inhibiting atherosclerosis in rabbits illustrated in Example III, similar plasmid constructs may be made for other vertebrates, including humans. Such plasmids encode an immunogenic fusion polypeptide comprising a universal or broad range T cell epitope, such as from tetanus toxoid or diphtheria toxoid, linked in the same reading frame to at least one, more preferably two, B cell epitopes of the endogenous CETP of the individual. An example of a plasmid-based vaccine for endogenous human CETP contains a DNA sequence encoding a translation initiating methionine linked to a TT polypeptide, such as in nucleotides 10-54 of SEQ ID NO:5, which is linked in the same reading frame (with or without intervening linker sequences) to a DNA sequence encoding regions of human CETP analogous to those used in the rabbit CETP plasmid-based vaccine, such as nucleotides 1045-1101 and 1381-1428 of SEQ ID NO:3 encoding amino acids 349-367 and 461-476 of SEQ ID NO:4, respectively. Preferably, the DNA sequence in the plasmid for use as a vaccine against human endogenous CETP also includes regions as shown in FIG. 5, such as translational start and stop codons and flanking

restriction endonuclease sites that are commonly employed for plasmid construction and gene expression.

Thus, one of skill in the art would be motivated to modify the peptide immunogens of Suzuki et al., to provide chimeric peptides wherein the beta-amyloid portion of Suzuki is linked to the diphtheria toxoid portion of Stevens or Lehrer. Such modification results in a chimeric peptide comprising a first portion wherein the first portion is linked to the amino terminus of the free N-terminus of a naturally occurring internal peptide cleavage product which when naturally occurring in a mammal is derived from a precursor protein and a second portion comprising a T helper cell epitope capable of binding multiple MHC molecules. In addition, Stevens teaches that such immunogenic peptides may be provided in an immunogenically effective amount to produce antibodies via administration with adjutants including alum. One of skill in the art would have been motivated to make such modifications in order to enhance the immunogenicity of the beta-amyloid peptides in order to obtain antibodies suitable for detection and diagnosis of Alzheimer's disease as taught via Suzuki, Lehrer, and Stevens cumulatively. Thomas evidences that diphtheria toxoid would be a suitable carrier for provoking antibody responses via providing T helper cell epitopes that bind to multiple MHC molecules. One of skill in the art would have expected success using such combinations based upon the reference's teachings of enhanced immunogenicity and the optimal carrier properties of diphtheria toxin with alum as taught by Stevens and Lehrer. Thus, the cumulative reference teachings anticipate the claimed invention.

Status of Claims

15. No claims are allowed.

16. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
August 8, 2003

LORRAINE SPECTOR
PRIMARY EXAMINER